UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,086	10/05/2005	Takaki Koga	14875-138US1/C1-A0214P-US	9242

26161 7590 03/10/2008

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
03/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,086	KOGA ET AL.	
	Examiner	Art Unit	
	MICHAEL SZPERKA	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/05/05, 5/22/06, 6/20/06, 3/22/07, 5/2/07, and 8/31/07 .

DETAILED ACTION

1. Applicant's election without traverse of Group I, drawn to antibodies and kits, claims 1-12 and 15 in the reply filed on December 21, 2007 is acknowledged.

Claims 13 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 21, 2007.

Claims 1-12 and 15 are under examination in the instant office action.

Information Disclosure Statement

2. IDS forms received 10/05/05, 5/22/06, 6/20/06, 3/22/07, 5/2/07, and 8/31/07 are acknowledged and have been considered. Note that the 5/22/06 IDS has been lined through since it is not a proper form and the application in question was not provided with the statement. Note that the published version of this application, namely US2006/0167230, has been cited on the accompanying 892 form in a manner that comprises a publication date and thus meets the requirements for items suitable for inclusion on IDS forms.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has broadly claimed antibodies that bind activated protein C (aPC) and have the functional properties of potentiating aPC activity and inhibiting aPC inactivation. The specification does provide working examples of such antibodies and the specification discloses the Fv and CDR sequences of said example antibodies. The epitope(s) on aPC that are bound by such antibodies do not appear to be disclosed. Dependent claims state that the claimed antibody need only comprise one CDR recited by SEQ ID number, or a sequence functionally equivalent thereto. The antibodies are further recited as being present in compositions for use in preventing and treating diseases.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., of record as AD on 11/20/07 IDS, see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al. of record as AE on the 11/20/07 IDS, see entire document, particularly the abstract and the middle of the left column of page 1982).

The instant claims that recite CDR sequences require the claimed antibody to comprise only one of the listed SEQ ID numbers, yet it is recognized in the art that all 6 CDR sequences contribute to binding. Given that even a single amino acid change in the CDR can abrogate binding and that by reciting that only one CDR is of a fixed sequence allows for random sequence at the remaining 5 CDRs, it appears that the breadth of applicant's claimed antibodies would not work. Note that due to the recitation of "functionally equivalent" the claimed antibodies need not comprise any sequence identity or similarity to any of the SEQ ID numbers recited in the claims. Antibodies that bind aPC are well known in the art, and it is known that their functional properties differ

with respect to the epitope of aPC that is bound by the antibody (Suzuki et al., of record). The instant specification does not appear to disclose information concerning the location of the epitope within aPC that when bound by an antibody, leads to the observed functional effects. Given that distinct epitopes give rise to distinct functional properties, that all 6 CDR sequences participate in antigen binding, and that even single point mutations in a CDR can disrupt binding, it appears that making mutants comprising only one recited CDR or "functionally equivalent" sequences are unpredictable and would require the skilled artisan to engage in undue experimentation to ensure that such antibodies maintain the recited functional requirements , especially since the identity of the epitope(s) within aPC bound by the antibodies of the working examples are not disclosed.

Additionally, the antibodies recited in the instant claims are recited as being used in compositions for the prevention of disease. The term “prevention” reasonably encompasses 100% efficacy, yet no in vivo data of any sort has been provided to substantiate that administration of the recited antibodies does indeed prevent diseases, such as sepsis, in 100% of patients. It is known however that administration of aPC can be used to treat various diseases (see for example Grinnell et al., US Patent 6,037,322) and as such an antibody that prevents aPC (either naturally occurring of exogenously administered) from being inhibited would presumably behave similarly in treating disease.

Therefore, given the breadth of the claimed invention, the guidance and disclosure of the instant specification, and the teachings of the prior art, a skilled artisan would be unable to make and use the full breadth of the instant claimed invention without conducting additional unpredictable research.

5. Claims 1-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a broad genus of antibodies that comprise the activities of binding activated protein C (aPC), potentiating an activity of aPC, and inhibiting the inactivation of aPC. To support such a broad genus, applicant has disclosed antibodies which comprise the CDRs recited by SEQ ID number in claim 6 which comprise the recited functional activities. The epitope(s) or structure(s) within aPC that are bound by antibodies to give rise to the recited functional properties is not disclosed.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a

mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the structure bound by the claimed genus of antibodies (other than that it is somewhere on aPC) is not disclosed. The structures of the disclosed antibodies are not representative of the structures of the claimed genus since the claimed antibodies are not limited to the recited sequences. It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al. PNAS USA, 1982, 79:1979-1983, see entire document, particularly the abstract and the middle of the left column of page 1982). However, the instant claims either recite no sequences, or as in the case of dependent claim 6, recite that the claimed antibodies need only comprise one of the recited sequences or a sequence "functionally equivalent thereto". As such, applicant clearly seeks to claim antibodies comprising diverse CDR sequences that are not limited to those recited. Given that even a single amino acid change in a CDR can eliminate antigen binding, it does not appear that the disclosed sequences are representative since the specific structures that must be maintained in the CDRs to ensure functional activity do not appear to be disclosed. Further, the precise epitope within aPC, that when bound by an antibody gives rise to the recited functional properties, is also not recited. As such, it does not appear that the specification correlates binding of antibodies to aPC at a specific epitope to functional activity, and the structure of the disclosed antibodies is not representative because the structure of the claimed genus can vary in undisclosed,

unpredictable ways.

Therefore, it appears that a skilled artisan would reasonably conclude that the broad genus of antibodies claimed by applicant lacks adequate written description and thus applicant was not in possession of the entire breadth of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. (of record).

Suzuki et al. disclose antibodies that bind human activated protein C (see entire document, particularly the abstract). One of their antibodies, MCF-1, blocked the inactivation of activated protein C (aPC) by protein C inhibitor (PCI) (see particularly Figure 6). It is known in the art that aPC is rapidly inhibited by PCI (see lines 16-25 of page 2 of the instant specification). Since MCF-1 inhibits the inactivation of aPC, MCF-1 potentiates (i.e. helps) aPC activity since said activity is not diminished by PCI. The antibodies of Suzuki et al., including MCF-1, are disclosed in compositions comprising the pharmaceutically acceptable carrier Tris-HCl with protein C and aPC (see particularly page 130).

It is noted that some of the instant claims recite intended use limitations, such as "can be used to prevent or treat a disease". For product claims, intended use is not accorded patentable weight unless the intended use alters the structure of the claimed product in some manner. Since the prior art compositions comprise all of the structural elements of the claimed composition (i.e. antibody, aPC, and pharmaceutically acceptable carrier) and the recitation of disease treatment does not appear to add any

structural elements or constraints, the prior art compositions anticipate those that are instantly claimed.

It is also noted that Suzuki et al. do not disclose the sequence of their antibodies. Given that antibodies bind antigens via their complementarity-determining regions (CDRs), that claim 6 recites antibodies comprising "functionally equivalent" CDRs, and that the MCF-1 antibody of Suzuki et al. meets the functional activities recited in the claims, MCF-1 comprises CDR sequences that are "functionally equivalent" to those recited in claim 6.

Therefore, the prior art anticipates the claimed invention.

8. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Grinnell et al. (US Patent 6,037,322).

Grinnell et al. disclose kits comprising activated protein C, packaging material, and printed instructions (see entire document, particularly lines 54-60 of column 2 and claim 12). Claim 15 recites that "the kit comprises (a) at least one selected from the group consisting of protein C, activated protein C, and an antibody of claim 1". As such, the kit can minimally comprise protein C alone, activated protein C alone, or an antibody alone. Note that as per MPEP 2112, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)".

Therefore the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 7, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. (of record) in view of Zuk et al. (US 4,208,479).

The teachings of Suzuki et al. have been discussed supra. These teachings differ from the instant claimed invention in that their antibodies are not disclosed as part of a kit.

Zuk et al. teach that providing reagents, such as antibodies and antibody fragments, in kits offer the advantages of substantial convenience and enhanced accuracy when performing methods involving said reagents (see entire document, particularly from line 20 of column 22 to line 27 of column 23).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to place the antibodies and compositions of Suzuki et al. into a kit. Motivation to do so comes from the teachings of Zuk et al. that providing reagents in kit form provides the advantages of increased convenience and accuracy when performing immunological methods, such as those disclosed by Suzuki et al.

It is noted that the kit is recited as also comprising a recording medium comprising a description. All kits routinely come with directions, and as per MPEP 2112, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)".

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL SZPERKA whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka, Ph.D./
Primary Examiner, Art Unit 1644